UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte SUJIT K. BASU, JEFFREY HRKACH, MICHAEL LIPP, KATHARINA ELBERT and DAVID A. EDWARDS

Appeal No. 2005-1152
Application No. 10/202,616

ON BRIEF

Before WILLIAM F. SMITH, SCHEINER and MILLS, Administrative Patent Judges.

MILLS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. §134 from the examiner's final rejection of claims 1-47, which are all of the claims pending in this application.

Claim 1 is representative of the claims on appeal and appears as set forth below.

1. A method for delivery via the pulmonary system comprising:
administering to the respiratory tract of a patient in need of treatment, prophylaxis or diagnosis an effective amount of particles comprising:
a bioactive agent in association with a charged lipid wherein the charged lipid has an overall net positive charge, the agent has an overall net negative charge upon association, the agent is not a nucleic acid and wherein release of the agent is sustained.

The prior art references relied upon by the examiner are:

Unger et al. (Unger)	5,830,430	Nov. 3, 1998
Hanes et al. (Hanes)	5,855,913	Jan. 5, 1999
Szoka, Jr. et al. (Szoka)	5,811,406	Sept. 22, 1998
Zuckermann et al. (Zuckermann)	6,251,433	June 26, 2001

Grounds of Rejection

Claims 1-8, 24, 27-28, 32, 36-40 and 43-44 stand rejected under 35 U.S.C. 102(b) as anticipated by Unger.

Claims 1-24, 32-40, 43 and 45-57 stand rejected under 35 U.S.C. 103(a) for obviousness over Hanes in view of Szoka.

Claims 25-31, 41-42 and 44 stand rejected under 35 U.S.C. 103(a) for obviousness over Hanes in view of Szoka in further view of Zuckermann.

We reverse these rejections.

DISCUSSION

35 U.S.C. § 102(b)

Claims 1-8, 24, 27-28, 32, 36-40 and 43-44 stand rejected under 35 U.S.C. 102(b) as anticipated by Unger.

"It is well settled that a claim is anticipated if each and every limitation is found either expressly or inherently in a single prior art reference." Celeritas Techs. Ltd. v.

Rockwell Int'l Corp., 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522 (Fed. Cir. 1998). In addition, "An inherent structure, composition or function is not necessarily known. . . . Insufficient prior understanding of the inherent properties of a known composition does not defeat a finding of anticipation." Atlas Powder Co. v. IRECO Inc., 190 F.3d 1342, 1349, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999).

Prior to discussion of the prior art, we must interpret claim 1 before us. Claim 1 recites a method for delivery via the pulmonary system comprising: administering to the respiratory tract of a patient in need of treatment, prophylaxis or diagnosis an effective amount of particles comprising: a bioactive agent in association with a charged lipid wherein the charged lipid has an overall net positive charge, the agent has an overall net negative charge upon association, the agent is not a nucleic acid and wherein release of the agent is sustained. The specification, page 8, lines 19-23, states that the "particles suitable for pulmonary delivery can comprise a therapeutic, prophylactic or diagnostic agent which possesses an overall net negative charge in association with a lipid which possesses an overall net positive charge" (emphasis added). Thus, we interpret the phrase "the agent has an overall net negative charge

upon association" in claim 1 to mean that the bioactive agent has a negative charge.[1]

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[1] Note that the phrase "upon association" when read in context, that is with the meaning set forth in the specification, does not mean when the bioactive agent is in association with the charged lipid that the complex has an overall negative charge or that the bioactive agent retains a negative charge.

It is the examiner's position that (Paper No. 6, pages 2-3):

> Unger teaches cationic lipid compounds which comprises [sic] at least two cationic groups. The cationic lipid compounds are particularly suitable for use as carriers in intracellular delivery of bioactive agents, including pharmaceuticals and genetic material (col. 5, lines 13-38). Cationic lipid compound refers to a lipid which comprises a cationic group and which functions generally as a positively charged ion, for example, in solution (col. 8, lines 39-44). Bioactive agent refers to a substance which is capable of exerting a biological effect [sic, and?] is preferably therapeutic in nature. The bioactive agents may be neutral or positively or negatively charged. Preferably the bioactive agents are negatively charged. Examples of suitable bioactive agents include proteins (col. 9, lines 43-57). ["]In combination with["] refers to the incorporation of a bioactive agent with a cationic lipid compound. The cationic lipid compound can be combined with the bioactive agent in any of a variety of different ways such as hydrogen bonding, covalent bonding (col. 10, lines 15-38).
>
> Unger discloses that a wide variety of materials which act to stabilize the composition may be added. Also, the intracellular delivery of bioactive agents through the use of cationic lipid compositions may be enhanced by the presence of a gaseous substance. The preferred gaseous precursor is a salt such as alkali metal salt. Examples of the gaseous precursor materials include potassium carbonate, sodium carbonate, magnesium bicarbonate (col. 23, lines 22-29., col. 24, lines 1-15).

According to the examiner, "Unger also discloses that the formulations can be administered to a patient in a variety of forms adapted to the chosen route of administration, namely, parenterally, orally, pulmonary inhalation, nasal inhalation, etc (col. 27, lines 1-10). The weight ratio of cationic lipid compound to bioactive agent is preferably from about 1:1 to about 15:1, with a weight ratio of about 5:1 to about 10:1 being more preferred (col. 27, lines 35-50)." Paper No. 6, page 3.

Appellants concede "that there may be some combinations of the agents and excipients generically disclosed by Unger that will result in a sustained release profile

upon pulmonary delivery, with or without facilitating intracellular uptake. [But] [e]ven assuming that this is true, the caselaw [sic] does not support a finding of anticipation based upon the possibility that a prior art composition possesses a limitation or property recited in the claims." Reply Brief, page 2.

More particularly, appellants argue that, "the Examiner relies only upon a broad *generic* disclosure of selected components of the prior art to support the rejection. The broad generic disclosure permits a nearly indefinite number of combinations, which requires picking and choosing among multiple variables, and does not *anticipate* the present claim. Further, reliance on the doctrine of inherency to satisfy the limitation that the composition possesses a sustained release profile is misplaced." Reply Brief, pages 5-6. We agree with appellants that the disclosure of Unger is not an anticipation of the subject matter of claim 1.

We acknowledge that Unger does broadly disclose that its bioactive agent may possess any charge including neutral, positive or negative charges. Unger also specifically discloses that negatively charged bioactive agents are preferred. Col. 9, lines 50-52.

On the other hand, we agree with appellants that the many variables present within the disclosure of Unger weaken any alleged prima facie case of anticipation alleged by the examiner. For example, to meet the limitations of claim 1, the negatively charged bioactive agent cannot be a nucleic acid. But Unger teaches that the negatively charged bioactive agent may be selected from proteins, vitamins, steroids,

polyanions, nucleosides, polynucleotides and diagnostic agents such as contrast agents. Moreover, nucleic acids are described as "particularly suitable" (col. 25-26) and Unger's working examples are all directed to delivery of genetic material. Next, one of ordinary skill in the art must focus on providing sustained release pulmonary inhalation from varied, different and distinct methods of administration. Unger discloses a broad range of administration methods, including parenteral administration methods including intravenous, intramuscular, interstitially, intraarterial, subcutaneous, intra ocular, intrasynovial, transepithelial, transdermal, pulmonary via inhalation, ophthalmic, sublingual and buccal, topical, dermal, ocular, rectal, and nasal inhalation via insufflation. Unger, col. 27, lines 2-10. Even further, the ordinary artisan must determine which, if any, lipids with a net overall positive charge and a charge opposite to that of the bioactive agent, results in sustained release of the active agent when administered by a method of pulmonary inhalation.

We do not find that the examiner has pointed to any one specific example in the disclosure of Unger which anticipates the claimed method, or has indicated why the claimed choices would have been preferred from reading the disclosure of Unger and

would have provided sustained release when delivered by pulmonary inhalation.[2]

In our view, the examiner has not established by a preponderance of the evidence why one of ordinary skill in the art, with knowledge of Unger, would have been directed to select the particular negative charge and type of bioactive agent, and combine it with the a positively charged lipid, to result in a method of sustained release pulmonary inhalation of the active agent. Nor has the examiner directed our attention to a specific example within Unger which would inherently result in a sustained release when delivered via pulmonary inhalation. Thus, we agree with appellants that the examiner has failed to establish a prima facie case of anticipation on the facts before us. "Inherency ... may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981). The rejection of the claims for anticipation over Unger is reversed.

35 U.S.C. 103(a)

Claims 1-24, 32-40, 43 and 45-57 stand rejected under 35 U.S.C. 103(a) for obviousness over Hanes in view of Szoka. Claims 25-31, 41-42 and 44 stand rejected

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[2] The disclosure of Unger may not even be sufficient to support a prima facie case of obviousness. It is well settled that the "fact that a claimed compound and/or subgenus may be encompassed by a disclosed generic formula does not by itself render that compound or subgenus obvious". In re Baird, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994).

under 35 U.S.C. 103(a) for obviousness over Hanes in view of Szoka in further view of Zuckerman.

According to the examiner (Paper No. 6, page 4)

> Hanes teaches aerodynamically light particles incorporating a surfactant on the surface thereof for drug delivery to the pulmonary system, and methods for their synthesis and administration. The particles have a tap density less than 0.4 g/cm^3 and mass mean diameter between 5μm and 30μm. Exemplary surfactants include phosphoglycerides such as L-α-phosphatidylcholine dipalmitoyl (DPPC) (col. 3, line 57 to col. 4, line 66) suitable particulate 10, lines 24-49). Hanes lacks specific teachings on other suitable lipids.
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> Szoka teaches a method of stabilizing polynucleotide complexes by adding a cryoprotectant compound and lyophilizing the resulting formulation. Cationic lipids are useful in forming complexes to be cryoprotected and lyophilized. Conventional cationic lipids suitable for the formulations include phosphatidylethanolamine, dioleyloxyphosphatidyl-ethanolamine, 1,2 dimyristoyl-sn-glycero-3-ethylphosphocholine, 1,2 dioleyl-sn-glycero-3-ethylphosphocholine, etc (col. 6, lines 27-46). The formulations may also include buffers that can be removed during lyophilization (col. 6, lines 14-26). Charge ratios are disclosed in column 6, lines 1-9.

The examiner concludes (Paper No. 6, page 4) that

> [i]t would have been obvious to a person of ordinary skill in the art at the time the invention was made to have combined the method and formulations of Hanes on aerosolized, liposome associated drug particles with compositions of Szoka et al because of the disclosed benefits of various lipids in forming complexes and delivering therapeutic agents to respiratory system and because it provides patients and healthcare providers a wider selection of treatment and better absorption of actives systematically.

In our view the examiner has not established a prima facie case of obviousness over Hanes and Szoka. The examiner has not indicated, and we do not find, a charged lipid in particles for pulmonary delivery in the disclosure of Hanes. Hanes discloses a

lipid with a neutral charge and does not suggest a charged lipid can be substituted for a neutral charged lipid in its particles incorporating surfactants for pulmonary drug delivery. Thus, we do not find that Hanes provides an adequate reason, suggestion or motivation to select or combine the disclosure of Hanes with the cationic lipids described by Szoka.[3] Appellants argue that "the rejection does not explain why it would be obvious to turn to the teachings of Szoka to, for example, select DPePC as a lipid for manufacturing a non-nucleic acid formulation for pulmonary delivery and achieve a sustained release formulation." Reply Brief, page 7.

We agree. The rejection of the claims for obviousness over Hanes and Szoka is reversed.

According to the examiner, Hanes lacks specific teachings of suitable lipids, and the combined teachings of Hanes and Szoka, discussed above, lack specific teachings of carboxylic acid and metal salts. The examiner relies on Zuckermann for teaching compositions and methods for increasing the uptake of polynucleotides into cells. The composition comprises a lipoprotein, a polynucleotide binding molecule and a polynucleotide (col. 1, line 60 to col. 2, line 7). While teaching the synthesis of a polycationic agent, Zuckermann discloses use of aliphatic hydroxyl groups, carboxylic

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[3] Compare specification, page 44, showing (1,2-dipalmitoyl-sn-glycero-3-phosphocholine) DPPC (with neutral charge) and insulin as compared to sustained release obtained with positively charged DPePC (1,2-dipalmitoyl-sn-glycero-3-ethylphosphatidylcholine) and insulin; or page 48, showing negatively charged DSPG with albuterol sulfate is 4 times slower compared to DSPC, having no net overall charge.

acids, carboxy, thiol, amino and other reactive side-chain functionalities to minimize undesired side reactions (col. 31). Zuckermann also discloses that a pharmaceutical composition can contain a pharmaceutically acceptable carrier such as proteins, polymeric amino aids, amino acid copolymers etc. Pharmaceutically acceptable salts can be used therein, for example, mineral acid salts, phosphates, sulfates, and salts of organic acids (col. 32, lines 33-63).

The examiner concludes (Paper No. 6, page 6):

> [i]t would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the formulations and methods of the combined references by adding the additives such as carboxylic acids, salts and amino acids as taught by Zuckermann because of disclosed benefits of such additives in pharmaceutical formulations and reduction of undesired side reactions and improving stability of the product.

We have found no prima facie case of obviousness over Hanes in view of Szoka. We do not find the disclosure of Zuckermann overcomes the deficiencies of the primary combination of Hanes and Szoka. The rejection of claims 1-24, 32-40, 43 and 45-57 under 35 U.S.C. 103(a) for obviousness over Hanes in view of Szoka and the rejection of claims 25-31, 41-42 and 44 under 35 U.S.C. 103(a) for obviousness over Hanes in view of Szoka in further view of Zuckerman is reversed.

CONCLUSION

The rejection of claims 1-8, 24, 27-28, 32, 36-40 and 43-44 under 35 U.S.C. 102(b) as anticipated by Unger. The rejection of claims 1-24, 32-40, 43 and 45-57 under 35 U.S.C. 103(a) for obviousness over Hanes in view of Szoka is reversed. The

rejection of claims 25-31, 41-42 and 44 under 35 U.S.C. 103(a) for obviousness over Hanes in view of Szoka in further view of Zuckerman is reversed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

REVERSED

WILLIAM F. SMITH Administrative Patent Judge	)
TONI R. SCHEINER Administrative Patent Judge	) BOARD OF PATENT) APPEALS AND) INTERFERENCES
DEMETRA J. MILLS Administrative Patent Judge	)

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